REMARKS

Before this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-60, and 62-64 were pending. By this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-59, and 63-64 have been canceled and new claims 65-91 have been added. Therefore, if this Amendment is entered, an equal number of dependent claims will have been canceled and added and claims 60, 62, and 65-91 will be pending. It is believed that the added dependent claims all read on the elected species "angiogenic agent." In view of the above, the Applicant submits that it is appropriate to enter this Amendment.

Claims 60 and 62 have been amended to delete the recitation of non-elected species. Claims 60 and 62 now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Support for such a combination is found in the specification, as discussed below in the section directed to the rejections under 35 U.S.C. §112.

Support for new claims 65-91 is as follows:

New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 correspond to prior claims 10, 3, 17, 18, 19, 20, 24, 25, 34, 27, 42, 43, 44, 47, respectively. These prior claims have been deleted and these new claims added to address the objection in the Office Action that these prior claims did not depend from a preceding claim. New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 all depend from a preceding claim.

New claims 71-76 and 86-90 recite particular angiogenic agents. Support for the recitation of these particular angiogenic agents is found in the specification as follows:

Claims 71 and 86, page 18, lines 19-20.

Claims 72 and 87, page 18, line 20.

Claims 73 and 88, page 18, line 22.

Claims 74 and 89, page 18, line 21.

Claims 75 and 90, page 18, lines 20-21.

Claim 76, page 18, line 21.

Claims 77 and 91 recite that the angiogenic agent does not include nitric oxide synthase. Support for this recitation is found in the specification, at page 17, line 19 to page 18, line 16, where alternative therapeutic agents are positively recited: "Non-limiting examples of products and therapeutic agents of the invention include: ... nitric oxide synthase (NOS) ..." Such positive recitation nitric oxide as an alternative therapeutic agent provides support for a negative limitation with respect to nitric oxide synthase. See M.P.E.P. §2173.05(i):

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. *If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims*. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). (Emphasis added)

Election/Restrictions

The Office Action stated that species (2)-(35) and (2)-(37) in claims 60 and 62 were directed to non-elected subject matter.

Claims 60 and 62 have been amended to omit recitation of species (2)-(35) and (2)-(37).

Priority

The Office Action stated that the previous claims are not entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039) because "nothing in the specification [of U.S. Patent Application Serial No. 09/204,254] would lead one to the particular combination" of angiogenic agents set forth in the previous claims and therefore U.S. Patent Application Serial No. 09/204,254 lacks a written description of the previous claims (Office Action, paragraph bridging pages 3 and 4).

The claims have been amended to delete recitation of the combination of angiogenic agents recited in the previous claims. All the claims now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. To illustrate this, currently amended claim 60 is reproduced below, without the markings showing how it has been amended.

60. A medical device comprising:
a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:
(A) a therapeutic agent, where said therapeutic agent is an angiogenic agent, and
(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said

polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, where said polypeptide or protein is an angiogenic agent.

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in the paragraph at col. 5, l. 49 to col. 6, l. 22 of U.S. Patent No. 6,369,039, which reads in relevant part: "In addition, the polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated, include without limitation, angiogenic factors ... and combinations thereof."

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is also disclosed in the paragraph at col.4, l. 64 to col. 5, l. 48. This paragraph teaches which therapeutic agents can be in the coating. Polynucleotides (col. 4, l. 67 to col. 5, l. 4) and angiogenic agents (col. 5, ll. 15-16) are taught. The combination of polynucleotides and angiogenic agents is taught at col. 5, l. 44 ("and combinations thereof"). That the polynucleotides may encode angiogenic agents is taught at col. 5, ll. 62-65.

The present claims are therefore entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039).

Claim objections

The claims were objected to because the dependent claims did not depend from a preceding claim.

The claims have been amended so that all dependent claims depend from a preceding claim.

Claims 37 and 58 were objected to as being substantial duplicates.

Claims 37 and 58 have been canceled.

The rejection under 35 U.S.C. §112

The claims were rejected for failure to comply with the written description requirement because the "instant specification does not disclose the subgenus" of angiogenic agents set forth in the claims (Office Action, sentence bridging pages 6-7 and following sentence).

The claims have been amended and no longer recite the subgenus of angiogenic agents to which this rejection was directed. The claims as presently amended have written description support since the specification provides guidance which clearly leads the skilled person to the recited combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

The combination of a therapeutic agent comprising genetic material, e.g., a polynucleotide, with a non-genetic therapeutic agent is clearly disclosed at page 17, lines 6-8:

> The first therapeutic agent of this invention comprises genetic materials whereas the second therapeutic agent of the invention may comprise either genetic or non-genetic materials.

The reference to the "first therapeutic agent" in this passage would be understood in light of prior disclosures in the specification which teach that the "first therapeutic agent" is preferably a polynucleotide. See, e.g., page 5, lines 6-7 ("a first therapeutic agent comprising ... a first polynucleotide ..."); page 6, line 9 ("a first therapeutic agent comprising ... a first polynucleotide ..."). Thus, the passage at page 17, lines 6-8 would be understood as teaching the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent.

In the second paragraph after the above disclosure of the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent, there is a disclosure that both therapeutic agents can be angiogenic agents (page 18, line 1).

This is reinforced by original claim 33, which states that "said first therapeutic agent, said second therapeutic agent, ***or both***" can lead to the production of an angiogenic agent. Original claim 33 depends from original claim 26, which, in one of its embodiments, is directed to the combination of a polynucleotide and a protein. Thus, original claim 33 teaches that the Applicant contemplated the combination of a polynucleotide and a protein where the polynucleotide encodes an angiogenic agent and the protein is an angiogenic agent.

The skilled person is again directed to this combination at page 22, line 21 to page 23, line 6, where a preferred embodiment of the invention is disclosed as:

> A preferred embodiment of this invention is to provide treatment of vascular thrombosis and angioplasty restenosis, particularly coronary vascular thrombosis, and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis and restenosis, unstable angina, myocardial infarction and sudden death. The medical device and method of this invention can be used to treat patients having severe complications resulting from thrombus. Specific examples include patients with acute myocardial infarction (AMI) and patients that have failed PTCA (percutaneous transluminal coronary angioplasty) and have abrupt thrombotic closure of the targeted artery.

From this passage, the skilled person would recognize that the invention is designed to increase blood flow and thereby oxygen delivery to tissues, particularly to tissues sensitive to disruptions in cardiovascular perfusion. The skilled person would recognize that this can be accomplished through a local increase of blood flow by the development and expansion of blood vessels in an area of potential stenosis or thrombotic blockage, i.e., by angiogenesis. Thus, the skilled person is directed to the choice of "angiogenic agents" as the therapeutic agents of the invention.

Furthermore, in Example 7 on pages 28-29, the specification discloses an embodiment in which both therapeutic agents are "angiogenic agents." This example discloses a medical device comprising polynucleotides encoding VEGF protein and FAS Ligand protein.

The specification indicates that VEGF protein is a "promoter of endothelialization" (Example 7, page 29, line 3), i.e., an angiogenic agent. Moreover, it is well known in the art that VEGF protein is known to play a critical and central role in angiogenesis. FAS Ligand is also known to promote angiogenesis. See Biancone et al., Development of Inflammatory Angiogenesis by Local Stimulation of Fas In Vivo. J. Exp. Med. Volume 186, Number 1, July 7, 1997 147-152 (see, e.g., the summary, at page 147: "These findings suggest a role for Fas-Fas ligand interaction in promoting local angiogenesis and inflammation.")

Thus, Example 7 clearly directs the skilled person to the concept of practicing the invention wherein ***both*** therapeutic agents are angiogenic agents. Although Example 7 describes the use of two genetic therapeutic agents rather than the presently claimed combination of a genetic therapeutic agent and a non-genetic therapeutic agent, the combination of a genetic therapeutic agent and a non-genetic therapeutic agent is clearly described elsewhere (see discussion above) and would have been understood as being applicable to the teaching of Example 7 that both therapeutic agents can be angiogenic agents.

In view of the disclosures of the application discussed above, it is clear that the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is described in the application. Therefore, the present claims have written description support and it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §102

Certain of the previous claims were rejected as being anticipated by U.S. Patent No. 5,879,713 (Roth).

The Applicant respectfully traverses this rejection. The present claims require a polymeric coating on at least a portion of a medical device. Roth does not disclose a polymeric coating on a medical device. Instead, Roth discloses that a medical device (e.g., a catheter) can be used to deliver a polymer to a tissue so as to form a coating on the surface of the tissue. See col. 11, ll. 43-53:

> Local administration of a polymeric material can be performed by loading the composition in a balloon catheter, and then applying the composition directly to the inside of a tissue lumen within a zone occluded by the catheter balloons. The tissue surface may be an internal or external surface, and can include the interior of a tissue lumen or hollow space whether naturally occurring or occurring as a result of surgery, percutaneous techniques, trauma or disease. The polymeric material can then be reconfigured to form a coating or "paving" layer in intimate and conforming contact with the surface.

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Roth does not disclose this combination. Specifically, although Roth states that biologically active molecules include proteins, nucleic acid molecules, carabohydrates and "combinations thereof," Roth does not describe the specific combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent, as recited by the present claims. Accordingly, Roth does not anticipate the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Applicant notes that the present claims are not anticipated by U.S. Patent No. 5,652,225 (Isner). With the exception of one paragraph, the entire disclosure of Isner is directed to the use of hydrophilic polymers incorporating a single DNA encoding a protein, e.g., an angiogenic protein.

The exceptional paragraph occurs at col. 7, ll. 1-10. In this paragraph, Isner describes three additional methods of practicing his invention. The three methods involve certain combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors.

> In certain situations, it may be desirable to use DNA's [sic] encoding two or more different proteins in order [sic] optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF, can be used, and provides an improvement over the use of bFGF alone. Or an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously including angiogenesis, ...

The three methods described in this paragraph are:

Method 1: DNAs encoding two angiogenic proteins, i.e.,

DNA encoding an angiogenic factor + DNA encoding an angiogenic factor

Method 2: an angiogenic factor combined with other genes, i.e.,

An angiogenic factor + DNA encoding a non-angiogenic factor

Method 3: an angiogenic factor combined with gene products of other genes, i.e.,

An angiogenic factor + a non-angiogenic factor

The present claims all require the combination of a polynucleotide (e.g., DNA) encoding an angiogenic agent[1] with an angiogenic agent, i.e., an angiogenic factor + DNA encoding an angiogenic factor.

None of Isner's three methods is directed to an angiogenic factor + DNA encoding an angiogenic factor. This is shown in the following table. In the table, each of the possible combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors is represented by an entry at the intersection of the corresponding terms at the top and side of the table.

[1] For the purposes of this discussion, it is assumed that the term "angiogenic factor" used by Isner is the same as the term "angiogenic agent" as used in the present claims.

	DNA encoding angiogenic factors	**DNA encoding non-angiogenic factors**	**angiogenic factors**	**non-angiogenic factors**
DNA encoding angiogenic factors	Isner method 1		***The present claims***	
DNA encoding non-angiogenic factors			Isner method 2	
angiogenic factors	***The present claims***	Isner method 2		Isner method 3
non-angiogenic factors			Isner method 3	

It can be seen at a glance that there is no overlap between Isner and the present claims.

Isner goes on to provide a list of some of the products that can be used in his three methods: "including, for example, nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin (col. 7, ll. 9-10)."

The Applicant notes that nitric oxide synthase is not an "angiogenic agent" as that term is used in the present application. This can be understood from the manner in which these terms are used in the present application.

• Angiogenic agents and nitric oxide synthase are listed separately in the list of products and therapeutic agents of the invention at page 17, line 20 to page 18, line 17. Angiogenic agents are recited at page 18, line 1 while nitric oxide synthase is recited later, at page 18, line 6, in the midst of anesthetics and anti-coagulants, i.e., products that are undeniably not angiogenic agents. Such listings make no sense if nitric oxide synthase is an angiogenic agent.

• Page 18, line 18 to page 19, line 1, provides a list of angiogenic agents ("acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-

derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor"). Nitric oxide synthase is not part of this list.

• Where the present invention provides examples of the use of nitric oxide synthase, nitric oxide synthase is not used an angiogenic agent. Example 6 of the present application (pages 27-28) describes three experiments in which nitric oxide synthase is used for purposes other than angiogenesis (i.e., creating new blood vessels). In experiment 1 (page 27, line 21 to page 28, line 1), nitric oxide synthase is used to prevent restenosis. In experiment 2 (page 28, lines 2-6,), nitric oxide synthase is used to prevent progression and promote the healing of atherosclerotic lesions. In experiment 3 (page 28, lines 7-12), nitric oxide synthase is used to promote cell death in anti-cancer therapy.

Even assuming, *arguendo*, that nitric oxide synthase is considered to be an angiogenic agent by the art, the above teachings of the application make clear that nitric oxide synthase is not an "angiogenic agent" for the purposes of the present invention. The Applicant has been her own lexicographer and has defined the term "angiogenic agent" by implication so as to exclude nitric oxide synthase. Thus, any disclosure of nitric oxide synthase in Isner is not relevant to the present claims.

Even if nitric oxide synthase is considered to be an angiogenic agent, this would not mean that Isner discloses the present invention. If nitric oxide synthase is considered to be an angiogenic agent then it could serve the following roles in the three methods disclosed in Isner:

• either as one or both of the products encoded by the two DNAs of method 1

• as the angiogenic factor that is combined with "other genes" in method 2

• as the angiogenic factor that is combined with the gene products of "other genes" in method 3

In none of these cases would the result be within the scope of the present claims. In no case would the result be an angiogenic agent combined with a DNA encoding an angiogenic agent.

Furthermore, Isner does not anticipate claims 71-76 and 86-90, which are directed to combinations of particular angiogenic agents with DNA encoding those particular angiogenic agents since Isner does not disclose such combinations.

In view of the above, it is clear that Isner does not anticipate the present claims.

The rejections under 35 U.S.C. §103

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Branellec also does not disclose this combination. Since Roth and Branellec lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Branellec do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec) and further in view of Vincent-Lacaze et al., 1999, J. Virol. 73:1949-1955 (Vincent-Lacaze).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth and Branellec do not disclose this combination. Vincent-Lacaze also does not disclose this combination. Since Roth, Branellec, and Vincent-Lacaze lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth, Branellec, and Vincent-Lacaze do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,833,651 (Donovan).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Donovan also does not disclose this combination. Since Roth and Donovan lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Donovan do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Office is authorized to charge any fees or credit any overpayments that may be associated with the filing of this paper to Kenyon & Kenyon's Deposit Account No. 11-0600. The Applicant hereby also makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this

application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,
KENYON & KENYON

ZEBA Ali for

11-17-05
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